Office of Drug Safety

MEMO

To: Daniel Shames, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-400

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

CC: Diane Moore
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: March 8, 2002

Re: ODS Consult 01-0181-1; Estrasorb (Estradiol Transdermal [redacted]); NDA 21-371

This memorandum is in response to a February 13, 2002, request from your Division for a review of the proprietary name, Estrasorb. The expected goal date for this application is April 29, 2002.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Estrasorb since we conducted our initial review on January 3, 2002 (ODS consult 01-0181), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

The Division of Medication Errors and Technical Support (DMETS) considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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/s/

Scott Dallas
3/11/02 09:28:41 AM
PHARMACIST

Carol Holquist
3/11/02 01:16:12 PM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Medical Errors and Technical Support: Attention: Dr. Phillips/Sammie Beam HFD-400 PKLN bldg Room 15B-03			FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Diane Moore 17B-45	
DATE: February 13, 2002	IND NO.:	NDA NO.: 21-371	TYPE OF DOCUMENT : N	DATE OF DOCUMENT: June 29, 2001
NAME OF DRUG: Estrasorb™	PRIORITY CONSIDERATION: Routine		CLASSIFICATION OF DRUG: estrogen	DESIRED COMPLETION DATE: March 28, 2002

NAME OF FIRM: Novavax, Inc.

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE--NDA MEETING	RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	OTHER *(SPECIFY BELOW)*:
MEETING PLANNED BY		X Tradename review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	CHEMISTRY REVIEW
END OF PHASE II MEETING	PHARMACOLOGY
CONTROLLED STUDIES	BIOPHARMACEUTICS
PROTOCOL REVIEW	OTHER:
OTHER:	

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS (List below)	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a follow-up on the tradename review for NDA 21-371. The established name has been revised. The name accepted by DRUDP is "Estrasorb (estradiol topical emulsion)." The goal date for this supplement is April 29, 2002. Reviews need to be done by March 29, 2002. The sponsor has committed to revise their labeling in accordance with the new established name. The proposed labeling has not been received. It will be forwarded to you when it arrives. If you have any questions, please call Diane Moore at 7-4236.

cc: Original NDA 21-371
HFD-580/Div. Files
HFD-580/Diane Moore

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Diane V. Moore
2/13/02 10:51:55 AM

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 31 2002

Charles H. Miller, M.D., Ph.D.
1 North Brookwood
Hamilton, Ohio 45013

Dear Dr. Miller:

On December 13, 2001, Mr. Joseph X. Kaufman representing the Food and Drug Administration (FDA), met with your representative, to review your conduct of a clinical study (protocol E99-1) of the investigational drug Estrasorb (estradiol hemihydrate), performed for Novavax, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kaufman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

CFN: 3000209558
Field Classification: NAI
Headquarters Classification:
__X_ 1) NAI
_____2) VAI- no response required
_____3) VAI- response requested
_____4) OAI

Deficiencies noted: None

cc:
HFA-224
HFD-580 Doc.Rm. NDA #21-371
HFD-580 Review Div.Dir.
HFD-580 MO
HFD-580 PM
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File #10532
HFD-46 GCP Reviewer/Lewin
HFD-46 GCPI Br Chief/Martin
HFD-46 CSO/Ibarra-Pratt
HFR-CE450 DIB/Carol Heppe
HFR-CE450 Bimo Monitor/Eastham
HFR-CE450 Field Investigator/Kaufman

r/d: CL:01-28-02
reviewed:JM:1/30/02
f/t:ju:1/30/02
o:\cl**Miller N21371 Jan02 NAI.doc**

Note to Rev. Div. M.O.

This routine clinical inspection was conducted in support of pending NDA #21-371 and focused on protocol E99-1. Thirty subjects were enrolled at this site; one subject was withdrawn, due to non-compliance.

An in-depth audit was conducted on records for eight subjects; consent documentation was reviewed for all subjects. No objectionable conditions were noted during the inspection.

Data appear acceptable.

Redacted 3

page(s) of trade secret and/or confidential commercial information (b4)

1/22/02

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-400)

DATE RECEIVED: 08/10/2001	**DUE DATE:** 01/22/2002	**DMETS CONSULT #:** 01-0181

TO: Daniel Shames, MD
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Diane Moore
Project Manager
HFD-580

PRODUCT NAME: Estrasorb (estradiol) 1.74 gram pouches **NDA #** 21-371	**NDA Holder:** Novavax, Inc.

SAFETY EVALUATOR: Marci Lee, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, Estrasorb, to determine the potential for confusion with approved proprietary and established names well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name, Estrasorb. DMETS recommends revising the labels and labeling as outlined in section III of this review.

APPEARS THIS WAY
ON ORIGINAL

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 3, 2002

NDA NUMBER: 21-371

NAME OF DRUG: Estrasorb (estradiol [redacted]

NDA HOLDER: Novavax, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products for assessment of the proposed proprietary drug name, Estrasorb, regarding potential name confusion with other proprietary and/or established drug names.

PRODUCT INFORMATION
Estrasorb (estradiol transdermal [redacted], is indicated for treatment of moderate to severe vasomotor symptoms associated with menopause. The recommended dosage for Estrasorb is [redacted] two 1.74 gram foil pouches daily [redacted]. Estrasorb is applied to the skin of the anterior thigh and calves of both legs each morning to provide systemic delivery of estradiol 0.05 mg of estradiol per day. Estrasorb will be available as [redacted] 1.74 gram foil laminated pouches.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names, which sound or look similar to *Estrasorb* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[iv]. The Saegis[vi] Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies to simulate the prescription ordering process, in order to evaluate the potential for errors in handwritten and verbal communication of the name.

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[i] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2001).

[ii] Facts and Comparisons, 2001, Facts and Comparisons, St. Louis, MO.

[iii] The Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 1998-2001, and online version of the FDA Orange Book.

[iv] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=ki4gp0.1.1

[vi] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, *Estrasorb*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Two proprietary names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Estrasorb. These products are listed in the table, along with the dosage forms available and usual FDA-approved dosage.

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	
Estrasorb	**estradiol** **1.74 gram pouches**	**two 1.74 gram pouches daily,** **Estrasorb is applied to the skin of the thigh and calves of both legs each morning to provide systemic delivery of 0.05 mg estradiol daily.**	
Estratab	Esterified estrogens 0.3 mg, 0.625 mg, 2.5 mg oral tablets	0.3 mg to 1.25 mg PO daily, administer cyclically.	Look-alike Sound-alike
Estraderm	estradiol 0.05 mg/24 hours [10 cm^2] 0.1 mg/24 hours [20 cm^2]	Apply to skin twice weekly.	Sound-alike

* Frequently used, not all inclusive

2. DDMAC did not object to the use of the name, Estrasorb.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

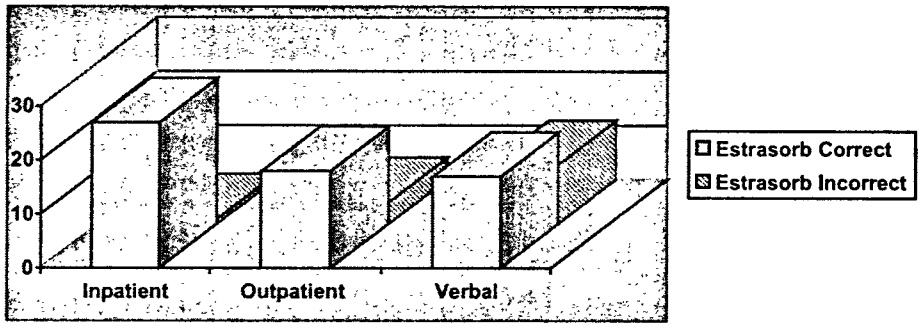
Three separate studies were conducted within FDA to determine the degree of confusion potential of Estrasorb with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 112 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescription for Estrasorb. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each participant was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Estrasorb	
Outpatient: Estrasorb — As directed #1	*Outpatient:* Estrasorb — As directed Dispense one
Inpatient: Continue Estrasorb as ordered	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Estrasorb" response	Other response
Written: Inpatient	38	28 (74%)	27 (96%)	1 (4%)
Written Outpatient	35	22 (63%)	18 (82%)	4 (18%)
Verbal:	39	28 (72%)	17 (61%)	11 (39%)
Total:	112	78 (70%)	62 (79%)	16 (21%)



Among the two written prescription studies, 5 of 50 (10 %) participants interpreted the name incorrectly. Incorrect interpretations included *Estasorb, Estrasorg, Estrosone*, and *Estrosorb.*

Among the verbal prescription study participants for Estrasorb, 11 of 28 (39 %) participants interpreted the name incorrectly. However, none of the incorrect responses were marketed products and many of the incorrect responses were phonetically equivalent to Estrasorb. Most participants interpreted the name as *Estrosorb*. Other incorrect responses were *Estrasol, Estrasor, Estrazor, Estro-sorp, Extrasurf* and *Xtrasorb.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Estrasorb, the primary concerns raised by the expert panel were related to two look-alike and sound-alike names that already exist in the US marketplace, Estratab and Estraderm. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that

Estrasorb could be confused with Estratab or Estraderm. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names.

The primary concern of the expert panel was the prefix "Estra-" being common for many drug products. In addition, "Estra-" has the potential to be confused with the prefixes, "estro-" and "extra-". However, very few of these products actually look or sound similar to Estrasorb.

Estratab can look or sound similar to Estrasorb because they share "Estra-" and end with the letter "b". Although Estratab has various indications, it can be used to treat the symptoms of menopause, like Estrasorb. There is no overlap of dosage strengths, dosage forms, route of administration, which decreases the likelihood for confusion. It is also unlikely that these products would be stored near each other. Although these products could be ordered by the same prescribers and used in the same patient population, the risk for confusion is minimal. Patients receiving Estrasorb will receive a large carton containing four boxes of foil packets — Estratab is an oral solid dosage form that is typically dispensed in a prescription vial. Although it is possible for these products to be confused, especially if the patient is receiving the medication for the first time and does not know what to expect or has not been told how to use the medication; the overall risk for confusion is minimal.

estrasorb estratab Estrasorb Estratab

Estraderm and Estrasorb have potential for sound-alike confusion, mainly due to the common "Estra-" prefix. These products share a similar indication, prescribers and patient population; however, Estraderm is a patch that is applied twice weekly unlike Estrasorb, which is a — that is applied daily. Although, there is no overlap in dosage strengths, Estraderm and Estrasorb are designed to deliver the same amount of estradiol in a 24 hour period. Although they are both topical medications, it is possible that these products are not stored near each other in a pharmacy since patches and — may be separated.

Following review of the container labels, carton and insert labeling, DMETS believes the packaging and nomenclature for Estrasorb is error-prone. Prescribing Estrasorb will challenge practitioners with remembering how many pouches to apply each day rather than use the more familiar terminology of a dose including a milligram amount of estradiol. This dosing will likely generate a large number of prescriptions with the instructions, "Use as directed". Ambiguous dosing instructions leave a burden on the patients and caregivers, which increases the opportunity for medication errors. Additionally, prescribing of medications in terms of the number of containers of drug instead of the milligram amount can lead to confusion and patients can receive the wrong dose in error.

Although, it is not clear from the insert what percentage of the Estrasorb dose is actually absorbed systemically; it is noted that the system is designed to deliver 0.05 mg/day. Listing this information on the labels and labeling is consistent with other formulations of transdermal estradiol.

Consider revising the DOSAGE and ADMINISTRATION section to read: [

]

Revise the packaging design to minimize user error. Continue to provide sizes of Estrasorb to allow for titration of the dose, however consider dispensing a single carton of each. Reconsider available packet sizes. It may be safer to provide [ ] a 1.74 gram packet.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container label, draft carton, draft insert and draft patient package insert labeling for Estrasorb, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, in the interest of minimizing potential user error.

A. FOIL POUCH CONTAINER LABEL

1. The font of the "E" in ESTRASORB differs from the rest of the word so much that it is possible to overlook it entirely and see only "strasorb". Modify the font style of the "E" in Estrasorb to improve readability of the product name.

2. Continue to list the amount (grams) of Estrasorb in each container.

3. Include the dosage strength of estradiol (mg or percent) in each container. Please note that the dosage strength should be listed more prominently than the net quantity of drug in each container.

4. Include the milligrams/day of estradiol to be delivered systemically.

5. Include the qualitative amounts of all inactive ingredients.

6. If space permits, include a usual dose statement on the container label.

7. Since this product is to be dispensed to a patient, please assure that the packaging is child-resistant.

8. Reconsider available packet sizes. [ ] a 1.74 gram packet.

B. FOIL PACKET CARTON LABELING

1. See above comments from FOIL POUCH.

2. [ ]

C. CONTAINER AND CARTON LABELING

1. See comments from FOIL POUCH (section III. A.)

2. [ ]

3. Include a usual dose statement on the container and carton labeling.

D. INSERT LABELING

1. DESCRIPTION

   a. Consider deleting the [redacted] from the US package insert. Although [redacted] is not considered a dangerous abbreviation by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), it may introduce confusion.

   b. Define ' [redacted] [ ]

   c. To decrease confusion, consider using one term to describe the foil "packets" or "pouches". The cartons use "packet" and the insert uses "pouch" to describe the same item. Revise accordingly.

2. DOSAGE AND ADMINISTRATION

   a. Increase the prominence the following statement by using a bold font and moving it to the beginning of the section. "Any excess ESTRASORB [redacted] either hand should be massaged into the buttocks. ESTRASORB [redacted] should not be applied to the breasts or other areas above the waist. Upon completion of ESTRASORB application, both hands should be washed with soap and water to remove any residual estradiol."

   b. In an effort to simplify the dosing directions and minimize the risk of error, consider revising the usual dosage statement to read: [ ]

   c. Revise "gm" to read "gram".

   d. Include the unit of measure (gram) in the directions for the 1.74 **gram** foil packets.

   e. Include the dosage strength of estradiol (mg or percent) in the directions for the [redacted] 1.74 grams foil packets.

3. HOW SUPPLIED

   a. [redacted]

   b. Elaborate on statement "DO NOT STORE OPEN".

E. PATIENT INSERT LABELING

1. ESTRASORB FOIL-LAMINATED POUCHES

   Revise "gm" to read "gram".

2. APPLICATION OF ESTRASORB

   a. Increase the prominence of the following statements

      i. "If you forget to apply ESTRASORB just apply another dose as soon as you remember."

      ii. "Do not apply ESTRASORB to your breasts"

      iii "Please keep ESTRASORB out of reach of children"

   b. Include the following statement: "Any excess ESTRASORB — on either hand should be massaged into the buttocks. ESTRASORB — should not be applied to the breasts or other areas above the waist. Upon completion of ESTRASORB application, both hands should be washed with soap and water to remove any residual estradiol."

   c. Define [ ]

   d. Consider use of illustrations to facilitate patient understanding of instructions.

3. Include a statement regarding safe disposal of the foil packets and a warning to keep away from children and pets.

IV. RECOMMENDATIONS

A. DMETS has no objection to the use of the proprietary name, Estrasorb.

B. DMETS recommends implementation of the above labeling revisions in order to minimize user error.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, Pharm.D.
Safety Evaluator
Office of Drug Safety (DMETS)

APPEARS THIS WAY
ON ORIGINAL

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/s/

Marci Ann Lee
1/18/02 01:57:54 PM
PHARMACIST

Carol Holquist
1/18/02 03:13:19 PM
PHARMACIST

Jerry Phillips
1/22/02 08:15:34 AM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2/14/02

NDA 21-371

INFORMATION REQUEST LETTER

Novavax Incorporated
Attention: D. Craig Wright, M.D.
Chief Scientific Officer
12111 Parklawn Dr.
Rockville, MD 20852

Dear Dr. Wright:

Please refer to your June 29, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrasorb (estradiol topical emulsion) 2.5 mg/g.

We also refer to your submission dated June 29, August 8 and December 14, 2001.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide an explanation for the estradiol assay failures during stability studies ——
—— Without an explanation, an expiration date for the drug product cannot be given.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
2/14/02 01:59:46 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-371

2/1/02

Novavax
Attention: D. Craig Wright, M.D.
Chief Scientific Officer
12111 Parklawn Dr.
Rockville, MD 20852

Dear Dr. Wright:

Please refer to your June 29, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrasorb (estradiol topical emulsion) 2.5 mg/g.

We also refer to your submission dated June 29, August 8 and December 14, 2001.

We are reviewing the Chemistry, Manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Please provide information on the container closure system for storage of the drug substance.

2. Please adopt an infra-red (IR) identification test for acceptance of the drug substance.

Excipients

Please implement an assay specification for the surfactant polysorbate 80. Without this specification, lot-to-lot consistency in the penetration enhancement capability of the drug product can not be assured.

Drug Product

1. Please implement in-process control limits for particle size and homogeneity of estradiol throughout the batch during the manufacturing process. These controls are necessary to assure uniformity of estradiol and particle size throughout the batch.

2. Please adopt an in-process control for [redacted]

3. The drug product batches should be examined for the presence of [redacted] under the microscope. If [redacted] form as a function of time, please adopt a specification

for the number, allowed per unit dose. This is necessary, because the [redacted] of the drug is not available for absorption.

4. In order to prove that the assay is stability-indicating, you have conducted stressed studies using the Estrasorb [redacted] Stressed studies should be performed using the estradiol [redacted] to form degradation products to demonstrate that the estradiol assay method is stability-indicating by detecting the degradation products. The level of quantitation (LOQ) value provided for estradiol ([redacted]) in your assay method is satisfactory for the assay of estradiol; however, it is not adequate for the determination of estradiol-related substances in the drug product. Unless justified, the assay method for estradiol-related substances must be sensitive enough to [redacted] of the degradation product. The limit of detection for estradiol should be provided as suggested in the ICH-Q2A recommendation.

5. In the drug product specification for particle size determination, please provide information on the sample preparation, description of the control samples and equipment settings prior to analysis.

6. The test methods and acceptance criteria for content uniformity of the unit dose containers, and the homogeneity of the [redacted] containers should be included in the drug product specification.

7. For [redacted] should also be part of drug product specification.

8. Please include test methods and acceptance criteria for estradiol-related substances, and the release-rate test in the specification. All test methods should be submitted with the validation data.

9. With the current packaging design for the [redacted] of content. This is not acceptable, unless otherwise justified.

10. Please adopt an acceptance criterion for viscosity of the drug product.

11. The acceptance criteria for ethanol in the drug product should be justified based on the preservative-effectiveness test data.

12. Please commit to monitor the [redacted] on batch release and during stability for [redacted] lots and report the data to demonstrate that the polysorbate 80 is stable in the drug product. This one-time test can be conducted and the data can be submitted within one year post-approval.

Container/closure system

1. The [redacted] container should be provided for review. For submission requirements, please follow the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999."

2. Since the [redacted] component of the foil laminate is in contact with the drug product, please provide the extractable and leachable information for the foil pouch. Please also implement an identification test, preferably IR, for acceptance of the foil laminate. For submission requirements, please follow "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999."

Labeling

1. The pouch labels for [redacted] 1.74 gram unit doses should be modified as follows:

   a. The established name should be changed to "estradiol topical emulsion."

   b. The storage conditions should read "Store at controlled room temperature at 25° C (77 °F); excursions permitted to 15-30°C (59-86 °F)."

   c. The statement ' [redacted] should be changed to "Estrasorb contains estradiol." The amount of estradiol per gram should be included on the label.

   d. The font for the "E" in Estrasorb should be revised to make it more readable.

2. The labels for [redacted] 1.74 gram carton label should be modified as follows:

   a. The established name should be changed to "estradiol topical emulsion."

   b. The storage conditions should read "Store at controlled room temperature at 25° C (77 °F); excursions permitted to 15-30°C (59-86 °F)."

   c. The statement ' [redacted] ' should be changed to "Estrasorb contains estradiol."

   d. The amount of estradiol per gram should be included on the label. A complete list of inactive ingredients should be included on the carton label. The total amount of Estrasorb should be deleted from the carton label. The font for the "E" in Estrasorb should be revised to make it more readable.

3. The label for [redacted] should be modified as follows:

   a. The amount of estradiol [redacted] label.

b. The established name should be revised to "estradiol topical emulsion."

c. The storage conditions should read "Store at controlled room temperature at 25° C (77 °F); excursions permitted to 15-30°C (59-86 °F)."

d. The statement ' [redacted] ' should be revised to "Estrasorb contains estradiol." The font for the "E" in Estrasorb should be revised to make it more readable.

4. The label for the carton [redacted] modified as follows:

a. The amount of estradiol [redacted] and a complete list of inactive ingredients should be included.

b. The established name should be revised to "estradiol topical emulsion."

c. The storage conditions should read "Store at controlled room temperature at 25° C (77 °F); excursions permitted to 15-30°C (59-86 °F)."

d. The statement ' [redacted] " should be revised to "Estrasorb contains estradiol." The font for the "E" in Estrasorb should be revised to make it more readable.

5. In addition, please respond to the microbiology issues that were discussed in the microbiology guidance meeting held with representatives from your firm and the Division of Reproductive and Urologic Drug Products on January 25, 2002.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for
Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
2/1/02 04:06:44 PM

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-371

ADVICE LETTER 8/1/02

Novavax
Attention: Marvin Heuer, M.D.
VP, Scientific Affairs
8320 Guilford Rd. Suite C
Columbia Maryland 21046

Dear Dr. Heuer:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrasorb™ (estradiol topical emulsion).

We refer to your request for withdrawal of this application dated April 29, 2002. We also refer to your June 6, 2002, correspondence (IND 49,761 SN-000), requesting a meeting to discuss your application.

During the review of your submission we identified the following Clinical and Chemistry, Manufacturing and Controls deficiencies. You may respond to these deficiencies when you resubmit the NDA.

Clinical:

1. Submit the protocol for 2x24 (a total of 48-hours) residual estradiol and transfer potential study. This study should be designed to demonstrate the amount of residual estradiol at selected time intervals within a 24-hour post-application period, and the transfer potential of the residual estradiol found on the skin surface over another 24-hour post-application period. We recommend that this 48-hour study utilize 2.5 mg ESTRASORB applied to the top of the right thigh and 2.5 mg ESTRASORB applied to the top of the left thigh for a total of 5.0 mg ESTRASORB each 24-hour post-application period. An adequate number of female study subjects should be selected. In addition, the sponsor may consider the following: (a) including variables such as gender and weight in the transfer potential study to address issues such as transfer potential to a smaller person in contact (e.g. child) and (b) adding a residual testing component to the transfer study (wiping with a swab to test the residual remaining on the skin).

2. Submit the protocol for a single dose, parallel arm or cross-over, 24-hour PK study designed to demonstrate the effect of sunscreen on the absorption of ESTRASORB applied to the right and left anterior thigh areas. An adequate number of female study subjects should be selected. We recommend the following treatments:

   Treatment A:
   1) the application of sunscreen to the top of the right and left thigh areas,
   2) application of 2.5 mg ESTRASORB to the top of the right thigh and 2.5 mg ESTRASORB to the top of the left thigh for a total of 5.0 mg ESTRASORB,
   3) sun exposure,
   4) PK collected over a 24-hour period.

Treatment B:
1) the application of 2.5 mg ESTRASORB to the top of the right thigh and 2.5 mg ESTRASORB to the top of the left thigh for a total of 5.0 mg ESTRASORB,
2) sun exposure (please note any skin photosensitivity following sun exposure for the ESTRASORB group),
3) PK collected over a 24-hour period.

3. Although the planned NDA resubmission will not include [redacted] should you plan to submit this packaging configuration in the future we would require the following information: the findings from a 12-week vasomotor symptoms study utilizing the same study design, inclusion and exclusion criteria, efficacy analyses, and safety assessments as primary study E99-1. The issue of subject compliance with the use of the [redacted] would have to be fully addressed. You may consider the use of [redacted] . A proposal for an [redacted] could be submitted for review.

Chemistry:

1. Address deficiencies provided in the Form 483 by the inspector.

2. Content uniformity of estradiol in the drug product in the unit-dose packages should be established. This can be accomplished by conducting content uniformity test according to USP <905> for suspensions in single unit. Test method and method validation should be provided.

3. Homogeneity of estradiol [redacted] should be established. The test method and its validation should be provided. This can be accomplished by taking aliquots from top, middle and bottom from [redacted] for estradiol content.

4. The delivery accuracy beyond [redacted] should be established. This may be accomplished by changing the design of the [redacted]

5. Stability indicating HPLC assay method should be established. Estradiol impurities and related substances assay in the drug product should be conducted adequately. Test method validation should be provided.

   The stability indicating nature of the HPLC assay can be proved by conducting stressed studies with estradiol solution to form degradation products and by showing that the assay method is stability indicating; i.e. estradiol can be assayed accurately in the presence of the degradation products. The limit of quantitation [redacted] recorded in the estradiol assay method is satisfactory for assay of estradiol but not for the assay of degradation products. Please develop an assay method for degradation product with [redacted] as recommended in "Guideline for Industry, Q3B Impurities in New Drug Products". In addition, limit of detection for the assay method should be submitted.

6. Specific reason and remedy for assay failures during stability studies [redacted] should be provided.

7. Since polysorbate 80 could be a penetration enhancer, an assay specification for the surfactant polysorbate 80 should be adopted.

8. To assure homogeneity of estradiol throughout the bulk lot, the in-process control for estradiol

homogeneity in various portions of bulk estradiol emulsion should be established.

9. The drug product batches should be examined with a suitable test method for the presence of estradiol —. If — of estradiol form as a function of time during storage, an acceptance criterion for the number of — allowed per unit dose should be adopted.

10. Since this drug product is a topical product for systemic absorption, a specification for in vitro release rate should be adopted.

11. The extractable and leachable information for the foil laminate should be provided according to the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999" for review.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

/S/

Daniel Shames
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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ON ORIGINAL

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/s/

Daniel A. Shames
8/1/02 12:21:08 PM

Minutes of Teleconference

Date: March 20, 2002 **Time**: 12:20 - 1:15 PM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name**: Estrasorb™ [redacted] (estradiol topical emulsion)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS) [redacted]

External Constituent: Novavax, Inc.

Type of Meeting: Eight-Month Status/Labeling Meeting

FDA Lead: Dr. Shelley Slaughter **External Constituent Lead:** Dr. Craig Wright

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Paul Stinavage, Microbiologist, Office of New Drug Chemistry (ONDC) Microbiology Team HFD-805

External Participants:
D. Craig Wright, M.D. – Chief Scientific Officer, Novavax
Joan Brisker – Director of Regulatory Affairs and Quality Assurance, Novavax
Dr.Rita Patel Vice President, Regulatory Affairs, Novavax

Meeting Objective:
To discuss outstanding issues regarding the review of for NDA 21-371 for the relief of moderate-to-severe vasomotor symptoms and potential time-lines for completion of outstanding studies.

Background:
Information request letters were sent to the sponsor on February 1 and 14, 2002, and a telecon was held February 25, 2002, requesting additional information from the sponsor regarding chemistry, manufacturing and quality control issues. Additionally, the sponsor was asked for the following clinical information on March 11, 2002:

- definition of endometrial disorders listed under the urogenital body system in Panel 8.8.13.1, Volume 26, page 109 (i.e., what does this indicate?)

- if by chance it means the number of subjects with a TVUS greater than 4 mm at the end of the study, why does Table 10.0.0 in Volume 26, page 165 differ in numbers from Table 28,0.0 in Volume 27, page 141?

(See response to clinical questions below in **Post Meeting Addendum**).

Discussion Items:

- Microbiology
  - the sponsor clarified that the product that was tested in the anti-microbial effectiveness test in the March 7, 2002 submission was the to-be-marketed product and that USP protocol was followed during the testing; the sponsor was requested to follow-up the clarification with a submission to the NDA explaining what was used as the test article and what protocol was used

Decisions Reached:

- Clinical
  - the single-dose packages in the primary clinical trial were three 1.15 gm pouches; there is an absence of clinical data available for the 2-package dose packaging configuration and the
  - it needs to be demonstrated that the content of the drug product expressed in two of the 2-package configuration (1.75 gm each) equals the content of the drug product expressed in three of the 3-package dose configuration (1.15 gm each)
  - there is no clinical trial data related to the
  - no information has been submitted to the NDA on
  - residual estradiol levels E2000-1 study demonstrates the presence of residual estradiol from the 1.15 gm pouch after two hours and eight hours; additionally, the sponsor should clarify what the potential is for transference to another individual; the labeling has no instructions to wash application areas after applying a dose
- Chemistry, Manufacturing and Quality Control
  - in the February 1, 2002, Agency letter, the sponsor was asked to submit data on the content uniformity of the estradiol in the single-dose unit; the method and acceptance criteria for the single-dose unit should conform to USP 24 Chapter <905> (page 2001-2002)
  - the number of ; per pouch and ; should be investigated using using retained stability samples (no new stability studies are needed); configurations should be tested (the 1.15 gm pouch, 1.75 gm pouch ; storage samples should be used; the test method and acceptance criteria should be included along with the validation for the test; this is a critical review issue

- Note: any of the above items submitted at this time during NDA review would be considered as major amendments and could necessitate the extension of the PDUFA user fee goal date by three months (to July 29, 2002)
- the sponsor should provide the time-table for submitting the assay method for polysorbate 80 analysis and validation; three product lots should be tested; the sponsor indicated that they have contracted with — to start testing; — has done validation on the test method
- forced degradation studies of the estradiol component has not demonstrated that the sponsor can separate out different peaks relating to the different degradants in the product; instead, the Division recommends the sponsor use a solvent of their choice and stress the product with high temperatures and change the detection wavelength from — both acid and alkaline pHs should be utilized
- the proposed limit of quantitation [redacted] is not acceptable for related substances; [redacted] LOQ is the ICH recommendation
- the single-dose unit (1.15 gm pouch) failed the assay at several time-points during the stability studies; this needs to be explained; the rationale is needed to justify the shelf-life for the product

- Clinical Pharmacology and Biopharmaceutics
  - content consistency needs to be demonstrated between the 2-package dosing and the 3-package dosing regimen; the sponsor could address this with an experiment where the weights of the contents expressed from the two and three-package systems (e.g., 12 sets of each) respectively are compared; it was suggested that the sponsor may recruit women (preferably postmenopausal) for this experiment, however, this may not be an absolute requirement
  - an additional test to see individual variability should be conducted with the same subject doing replicate testing of the weight of the product from the sets of packaging configurations

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• submit clarification to the NDA as to the protocol and test subject in the microbial effectiveness test	Novavax	ASAP
• submit additional data from requested studies	Novavax	ASAP
• notify project manager of time-lines for data submissions	Novavax	ASAP
• send copy of meeting minutes to sponsor	DRUDP	1 month

{See appended electronic signature page} /S/

Signature, recorder

{See appended electronic signature page} /S/

Signature, Chair

Post Meeting Addendum: The sponsor replied to the clinical question posed in the background section of these minutes in a submission to the NDA dated March 18, 2002

drafted: dm/3.28.02/N21371SM32002.doc

Concurrence:

M.Rhee, T.van der Vlugt, P.Stinavage, S.Al-Habet 3.28.02/A.Mitra 4.3.02/A.Parekh 4/4/02

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/s/

Diane V. Moore
4/4/02 05:11:58 PM

Shelley Slaughter
4/5/02 09:56:40 AM
I concur

Meeting Minutes

Date: March 18, 2002 **Time**: 2:00 - 3:15 PM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name**: Estrasorb™ — (estradiol topical emulsion)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS) —

Sponsor: Novavax, Inc.

Type of Meeting: Nine-Month Status/Labeling Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Margaret Kober – Acting Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Paul Stinavage, Microbiologist, Office of New Drug Chemistry (ONDC) Microbiology Team HFD-805
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)

Meeting Objective:
To discuss the status of the reviews for NDA 21-371 for the relief of moderate-to-severe vasomotor symptoms and labeling comments for the application.

Background:
The NDA was received on June 29, 2001. The final reviews are due to the Medical Team Leader on March 29, 2002. The target date for circulating the action package is April 15, 2002

Decisions Reached:
- Clinical
  - Review pending
  - —
- Division of Scientific Investigations (DSI)
  - inspection of — pending
- Chemistry, Manufacturing and Quality Control
  - a teleconference has been scheduled with the sponsor for Wednesday, March 20, 2002 to discuss outstanding CMC issues

- content uniformity information for the single-dose package has not been received; the sponsor should clarify the timing for submitting this data; if it is submitted during this cycle, it would be considered a major amendment to the NDA
- explanation for the assay failure of the 1.15 gm pouch on stability has not been received
- a degredation product assay for the estradiol component has not been received
- limit of detection (LOD) for estradiol has not been received; the limit of quantitation (LOQ) value of [redacted] is not adequate; ICH recommends a [redacted] or below, unless justified
- extractability testing for the [redacted] and foil pouches including physical and biological reactivity tests has not been received
- information on related substances and degradation products has not been submitted; this issue could be dealt with as a Phase 4 commitment
- the in-process control assay chosen by the sponsor for homogeneity throughout the batch is not adequate

- EES
  - establishment evaluation system (EES) inspection is ongoing at the [redacted] manufacturing site
- Microbiology
  - information requested in the January 25, 2002, teleconference with the sponsor was received and reviewed; the product appeared to have passed the anti-microbial effectiveness test at 28 days; it needs to be verified that the Estrasorb product was the test item ([redacted]) and it also needs to be clarified how the test was performed
- Pharmacology
  - review pending
- Clinical Pharmacology and Biopharmaceutics
  - second draft on review completed; pending secondary review; Biopharm briefing day scheduled for April 18, 2002 at 3:00 PM
  - *in vitro* bridging data is needed comparing the amounts used in the to-be-marketed dosing (two larger single-packages) with the to-be-marketed [redacted] and the clinical trial data that utilized three smaller single-package dosing needs to be performed; this is an approvability issue
  - the graphs in the labeling in the Clinical Pharmacology section that are not consistent with other HRT labeling should be deleted
  - in the patient package insert, it should say to check with your healthcare provider if you have calcium problems instead of having two sections, one for hypercalcemia and one for hypercalcemia
- Biometrics
  - no comments; review pending
- DDMAC and DSRCS reviews
  - the labeling on the [redacted] " however, there are no instructions for [redacted] the product labeling or in the clinical section of the NDA; the discrepancy needs to be clarified
  - labeling comments from DSRCS for the patient package insert have been incorporated onto the [redacted]
- Regulatory
  - final reviews are due to Medical Team Leader by March 29, 2002; action package is due to Director by April 15, 2002

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• convey outstanding comments to sponsor	review team	at March 20, 2002 teleconference
• determine if extended review is necessary	review team	2 weeks

/S/

Signature, recorder

/S/

Signature, Chair

drafted: dm/3.28.02/N21371SM31802.doc

Concurrence:
M.Kober, T.van der Vlugt, P.Stinavage 3.28.02/A.Mitra 4/4/02
Response not received from S.Al-Habet, L.Stockbridge

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/s/

Diane V. Moore
4/4/02 05:09:05 PM

Shelley Slaughter
4/5/02 09:51:05 AM
I concur.

Meeting Minutes

Date: February 20, 2002 **Time**: 9:00 - 10:00 AM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name**: Estrasorb™ ___ (estradiol topical emulsion)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS)

Sponsor: Novavax, Inc.

Type of Meeting: Eight-Month Status/Labeling Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews for NDA 21-371 for the relief of moderate-to-severe vasomotor symptoms and labeling comments for the application.

Background:
The NDA was received on June 29, 2001. The final reviews are due to the Medical Team Leader on March 29, 2002. The target date for circulating the action package is April 15, 2002

Decisions Reached:
- Clinical
  - Review pending
  - the ___
  - second Safety Update has been submitted
- Division of Scientific Investigations (DSI)
  - the inspection of Dr. Charles Miller is complete; no violations found; inspection ___ pending
- Chemistry, Manufacturing and Quality Control
  - first review complete; content uniformity of estradiol in the single-dose unit and homogeneity in the were not conducted; the single-dose unit (1.15 gm pouch) failed the assay at several time-points during the stability studies

- Information Request letters were sent to the sponsor on February 1 and 14, 2002; response to the microbiology deficiencies discussed in the January 25, 2002, teleconference were requested in the February 1st letter
- if the sponsor has further questions regarding the CMC requests, a telecon can be scheduled
- the sponsor must submit the following information by March 15, 2002; if the information is not received by that date, the review of the information may need to be deferred to the next review cycle or the goal date extended
  - content uniformity for the single-dose package and homogeneity for the
  - explanation for the assay failure of the 1.15 gm pouch
  - a degredation product assay for the estradiol component
  - limit of quantitization (LOQ) (lower amounts of degredation products)
  - extractability testing for the foil pouches including physical and biological reactivity tests
- prior to the content being dispensed from the , the amount dispensed from
- an *in vitro* bridging data is needed comparing the amounts used in the to-be-marketed dosing (two larger single-packages) with the to-be-marketed multiple-dose packaging and the clinical trial data that utilized three smaller single-package dosing
- the labeling revisions (up to this point) have been incorporated into the labeling on the division
- establishment evaluation system (EES) report pending on the sponsor's first manufacturing site

- Microbiology
  - first review completed November 7, 2001; second review completed January 17, 2002; recommendation "not recommended for approval"
  - additional information requested in January 25, 2002 teleconference with the sponsor
- Pharmacology
  - Review pending per reviewer
- Clinical Pharmacology and Biopharmaceutics
  - Review pending; no issues to report; target review completion for March 29, 2002
  - additional information on the was submitted on February 20, 2002
  - labeling comments have been added to the labeling
- Biometrics
  - Review pending
- Regulatory
  - final reviews are due to Medical Team Leader by March 29, 2001; action package is due to Director by April 15, 2001

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• send labeling consult to DDMAC	Ms. Moore	1 week
• check on status of EES	Dr. Mitra	1-2 weeks

/S/
Signature, recorder

/S/
Signature, Chair

Post Meeting Addendum: Labeling consults were sent to DDMAC and DSRCS for physician and patient information inserts, respectively on February 22, 2002.

drafted: dm/2.28.02/N21371SM22002.doc

Concurrence:
T.van der Vlugt, S.Slaughter 2.5.02/A.Mitra 2.6.02/S.Al-Habet 3.13.02

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/s/

Diane V. Moore
3/13/02 11:38:44 AM

Shelley Slaughter
3/13/02 02:58:05 PM
I concur.

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Meeting Minutes

Date: January 25, 2002 **Time**: 2:00 - 3:00 AM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name**: Estrasorb™ [redacted] (estradiol topical emulsion)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS) [redacted]

External Constituent: Novavax, Inc.

Type of Meeting: Microbiology Guidance

FDA Lead: Dr. Paul Stinavage **External Participant Lead:** Dr. Craig Wright

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Peter Cooney, Ph.D. – Associate Director for Microbiology, Office of New Drug Chemistry (ONDC)
Microbiology Team HFD- 805
Paul Stinavage, Microbiologist, (ONDC; HFD-805)
Shelley Slaughter, M.D., Ph.D. – Team Leader, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Participants:
D. Craig Wright, M.D. – Chief Scientific Officer, Novavax
Joan Brisker – Director of Regulatory Affairs and Quality Assurance, Novavax (via telephone)

Meeting Objective:
To discuss the microbiology concerns regarding NDA 21-371.

Background:
A meeting was requested by the Division of Reproductive and Urologic Drug Products on January 23, 2002, to discuss microbiology issues.

Discussion Items:
Microbiology

- the topical product is not a sterile product; [redacted] effectiveness data to insure the microbiology integrity of the product throughout the life of the product; for [redacted], the sponsor should refer to USP 25 <51> for the criteria for the preservative test
- the unit-dose product configuration must show bacteriostasis to insure that microbiologic-mediated destruction of the active drug or severe contamination of the drug product does not occur

- the unit dose needs either to be sterile or to demonstrate bacteriostasis to meet NDA requirements
- additional testing above what has been submitted to the NDA is required
- a preservative may need to be added to the unit-dose and the product configurations
- the sponsor decided to avoid preservatives in the product because they felt that the preservatives would cause skin reactions
- the sponsor performed would inhibit microbial growth; the test was performed on solutions
- Estrasorb contains ethyl alcohol; if the ethyl alcohol passes the preservative challenge test, the ethyl alcohol specifications would most likely be set at testing of ethanol in water is insufficient to demonstrate preservative efficacy in the product
- the Division noted that ethyl alcohol solubilizes estradiol and warned that the amount of alcohol in the product may affect the absorbability of the active ingredient through skin
- over the shelf-life of the product, a few lots may fail microbiology testing; therefore, microbial contamination must be monitored during the shelf-life
- if preservatives are added, they should be tested at the lower limit of the product specification

Clinical Pharmacology and Biopharmaceutics

- if a preservative is added, the pharmacokinetic (PK) profile would be changed; drug absorption may be affected; the type of oil used also affects the absorption of the drug
- in the PK study, 973, the formulation was changed

Decisions Reached:

- the single-dose product does not have to show a positive preservative effectiveness test; however, it must be demonstrated that organisms do not proliferate over the life of the product; this is a safety issue
- the sponsor must show that the unit dose formulation does not support microbial growth
- the sponsor may perform the microbial test using USP antimicrobial preservative effectiveness test organisms and test for no growth; additional organisms should be added to the USP panel of test organisms, the additional organisms should include two additional molds and two additional Pseudomonads
- the sponsor will ; to perform Day 14 and Day 28 testing for preservative-effectiveness; an interim summary table will be submitted with the Day 14 data; a final report will be submitted upon completion; the report must be submitted by March 10, 2002
- the sponsor should add two other species of USP antimicrobial preservative effectiveness test organisms; the sponsor can call the Division with their choices of microbes for FDA concurrence once they check with
- the sponsor should submit their justifications for the proposed specifications for ethyl alcohol content

Regulatory

- the sponsor was reminded that additional information submitted to the NDA after January 29, 2002, may be considered a major amendment to the NDA; a major amendment could cause the PDUFA goal date to be extended three months; alternatively, the NDA could be reviewed with the information already submitted; in that case, information submitted after January 29, 2002, may be reviewed during the following review cycle; it is recommended that the sponsor submit the requested

information as soon as it is available because the targeted date for review completion in the Division is currently March 29, 2002

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• submit data from Day 14 microbial test at [redacted]	Novavax	2 weeks
• submit data from Day 28 microbial tests at [redacted]	Novavax	1 month
• submit follow-up data after Day 28 report is received for justification of preservative specifications	Novavax	prior to March 29, 2002

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

In a telephone conversation with Ms. Diane Moore on January 30, 2002, Dr. D. Craig Wright verified that the formulation submitted in the December 14, 2001, submission was the same final formulation submitted to the NDA.

drafted: dm/1.29.02/N21371TC12502.doc

Concurrence:

T.van der Vlugt 1.30.02/P.Stinavage 1.31.02/M.Rhee 2.7.02/A.Mitra 2.8.02
S.Slaughter, P.Cooney 2.12.02

APPEARS THIS WAY
ON ORIGINAL

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/s/

Diane V. Moore
2/13/02 08:49:21 AM

Paul Stinavage
2/13/02 08:53:33 AM

APPEARS THIS WAY
ON ORIGINAL

Redacted 10

page(s) of trade secret and/or confidential commercial information

(b4)

Meeting Minutes

Date: December 4, 2001 **Time**: 1:00 - 1:30 PM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name**: Estrasorb ([redacted] estradiol)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS) [redacted]

Sponsor: Novavax, Inc.

Type of Meeting: Six-Month Status Meeting

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective:
To discuss the status of the reviews for NDA 21-371 for the relief of moderate-to-severe vasomotor symptoms.

Background:
The NDA was received on June 29, 2001. The product is an emulsion of micelle nanoparticles containing estradiol hemihydrate. The NDA recommends the application of 7.5 mg of Estrasorb daily providing a dose of 50 µg/day of estradiol.

Decisions Reached:
- Clinical
  - Review pending
    - additional analysis data was received
    - no additional safety data was submitted in the 4-month Safety Update
- Division of Scientific Investigations (DSI)
  - inspections pending
- Chemistry, Manufacturing and Quality Control
  - Review pending
  - additional information was requested; the sponsor plans to submit the information by the third week of December 2001
  - the tradename being recommended is "Estrasorb™ [redacted] (estradiol transdermal emulsion)"

- Microbiology
  - Review completed November 7, 2001; no [redacted] testing of topical, [redacted] was included in the NDA submission
  - [redacted] data for the [redacted] has been requested; this is part of the information the sponsor plans to submit by the third week of December
- Pharmacology
  - No report
- Clinical Pharmacology and Biopharmaceutics
  - Review pending
  - the sponsor plans to submit additional information [redacted]
- Biometrics
  - Review pending
- Regulatory
  - the reviewers should be ready to discuss labeling at the next status meeting
  - final reviews are due to Medical Team Leader by March 29, 2001; action package is due to Director by April 15, 2001

Action Items:

• **Item:**	**Responsible Person**:	**Due Date**:
• check on status of OPDRA review	Ms. Moore	1 month

/S/
Signature, recorder

/S/
Signature, Chair

Post Meeting Addendum: On December 11, 2001, the chemists revised the naming convention for Estrasorb™ from ' [redacted] " to "Estrasorb (estradiol topical emulsion)."

drafted: dm/12.5.01/N21371SM12401.doc

Concurrence:
S.Slaughter 12.5.01/T.van der Vlugt 12.6.01/A.Mitra 12.10.01/A.Parekh 12.13.01
S.Al-Habet 12.18.01

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/s/

Diane V. Moore
12/20/01 11:43:47 AM

Shelley Slaughter
12/20/01 03:44:32 PM
I concur

Meeting Minutes

Date: August 8, 2001 **Time:** 1:00 - 1:35 PM **Location:** Parklawn; Room 17B-43

NDA: 21-371 **Drug Name:** Estrasorb ([redacted] estradiol)

Indication: reduction of moderate-to-severe vasomotor symptoms (VMS) [redacted]

Sponsor: Novavax, Inc.

Type of Meeting: NDA Filing Meeting

FDA Lead: Dr. Susan Allen

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dornette Spell-LeSane, NP-C. – Project Manager, DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Paul Stinavage, Microbiologist, (ONDC; HFD-805)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Constance Lewin, M.D. -Pharmacologist, Division of Scientific Investigation (DSI), GCP Branch I (HFD-46)
Dianne Spillman, Regulatory Health Project Manager, Division of Oncology Drug Products (DODP; HFD-150)

Meeting Objective:
To discuss the fileability of NDA 21-371 for the relief of moderate-to-severe vasomotor symptoms.

Background:
The NDA was received on June 29, 2001. The product is an emulsion of micelle nanoparticles containing estradiol hemihydrate. The NDA recommends the application of – of Estrasorb daily providing a dose of – /day of estradiol.

Decisions Reached:
- Clinical
  - Fileable

  - in the clinical trial, subjects applied three foil laminated sachets of lotion (each delivering 2.5 mg of estradiol) for a total of 7.5 mg of estradiol to the top of the right thigh, top of the left thigh, right calf and left calf with the residual applied to the buttocks; the NDA also contains [redacted] a package of two foil laminated pouches each delivering 3.75 mg of estradiol which needs to be rubbed into the skin for two minutes; clinical data from the use [redacted] two-pouch method of application were not included in the NDA
  - the product was reformulated in 1997 to increase the water content from [redacted] increase the stability of the product at room temperature; the pivotal trials used this new formulation; the sponsor did not submit bridging information for the [redacted] applications to the clinical application
- Division of Scientific Investigations (DSI)
  - all the study sites are in the United States; a request for clinical site audit will be forwarded to the DSI for [redacted]
- Chemistry, Manufacturing and Quality Control
  - Fileable
  - there are some deficiencies in the NDA that were discussed at the Pre-NDA meeting with the sponsor on June 22, 2001; additional information was requested from the sponsor on August 2, 2001, including:
    - the polysorbate 80 penetration enhancer and the particle size were not tested properly by the sponsor
    - the sponsor did not include a preservative challenge study in the NDA, as was requested in the Pre-NDA meeting
    - stability data for [redacted] was not submitted to the NDA
    - the sponsor did not submit the three validation packages and the Master Production batch record (this information was submitted on August 8, 2001)
- Microbiology
  - Fileable
  - the sponsor should submit preservative efficacy testing data for the [redacted] packaging; the current formulation may not pass preservative challenge for [redacted] however, a preservative challenge test is not required for the single-dose packaging
- Pharmacology
  - Fileable per the Pharmacology reviewer
- Clinical Pharmacology and Biopharmaceutics
  - Fileable
  - the manufacturing site was changed because the former site received a warning letter from the Agency; it was determined that there was no need for a bioequivalence study for the new manufacturing site because the sponsor used *in vitro* release formulation data to bridge the clinical and new manufactured formulations
  - it needs to be determined whether a comparison study for the [redacted] is needed
- Biometrics
  - Fileable
  - one placebo-controlled clinical study was submitted; the study was randomized by strata for intact uterus
- Regulatory
  - Fileable
  - Financial Disclosure information is adequate for review
  - Pediatric Waiver request was submitted for this application

- **Action Items:** none

/S/

Signature, recorder

/S/

Signature, Chair

Post Meeting Addendum:
The sponsor submitted the requested validation packages and the Master Production batch record on August 8, 2001. As of September 19, 2001, the sponsor has not submitted the requested stability data for the [ ] data from polysorbate 80 penetration enhancer tests, or particle size preservative challenge study data. The sponsor indicated that it would take some time to generate the data. The requested information that has not been submitted will be review issues.

drafted: dm/8.29.01/N21371FM8801.doc

Concurrence:
T.Rumble 8.29.01/K.Meaker, C.Lewin, A. Parekh, L.Stockbridge, T.van der Vlugt 9.4.01
S.Slaughter, A.Mitra 9.18.01/ S.Al-Habet, Allen 9.19.01
Response not received from D.Spillman, P.Stinavage, D.Spell-LeSane.